REMARKS

Claims 1-48 remain in this application. Claims 14 and 16 have been amended. Claims 15, 17 and 20-48 have been withdrawn.

Claims 14 and 16 have been amended to correct dependency and a typographical error, respectively. Claims 15, 17 and 20-48 have been withdrawn as a result of an earlier restriction requirement. In view of the Office's earlier restriction requirement, Applicants retain the right to present claims 15, 17 and 20-48 in a divisional application.

Rejections Under 35 USC § 112, Second Paragraph

The Office Action rejects claim 14 as being indefinite for lacking antecedent basis for the term "third disintegrant." Claim 14 has been amended to depend from claim 13, which contains antecedent basis for "third disintegrant." This amendment should obviate the pending rejection and Applicants respectfully request withdrawal.

The Office Action also rejects claim 16 as being indefinite for reciting "mannitol" and "microcrystalline cellulose" as "binding agents" when "these materials are described as 'bulking agents' in the specification." Applicants have amended claim 16 to recite "bulking agents" rather than "binding agents." Applicants teach mannitol and microcrystalline cellulose as bulking agents in the specification at paragraphs 47 and 48. This amendment should obviate the rejection and Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 USC § 103–Obviousness

The Office Action also rejects claims 1-14, 16 and 18-19 for obviousness over U.S. Pat. No. 6,346,533 to Cha *et al.* in view of U.S. Pat. No. 5,707,975 to Francois *et al.*, U.S. Pat. No. 6,509,038 to Baert *et al.* and U.S. Pat. Appln. Pub. No. 2003/0104066 to Murai *et al.*

The Office Action states that Cha teaches "a pharmaceutical composition for oral administration of itraconazole that exhibits improved solubility and bioavailability [and] that solubility of the drug is improved by dissolving the itraconazole in an organic solvent and dissolution drying the mixture to form particles." Further, the Office Action states that Cha teaches "a method of dissolution drying spray drying as well as via a fluid bed granulator" and "pharmaceutical excipients . . . in the dissolution-induced drying step, including a binder,

a disintegrant, a stabilizer, or another active material." Finally, the Office Action states that Cha teaches "granules having itraconazole distributed uniformly throughout" and formation of "a tablet or capsule" from the resulting granules.

The Office Action states that Cha does not teach: (1) hydrochloric acid; (2) a croscarmellose sodium disintegrant; (3) a polyvinyl pyrrolidone binding agent; or (4) non-spherical granules. The Office Action, however, asserts: (1) Francois teaches itraconazole with hydrochloric acid solution; (2) Baert teaches itraconazole with croscarmellose sodium; (3) Murai teaches granular itraconazole with polyvinyl pyrrolidone;" and (4) Cha, Francois, Baert and Murai, while not expressly teaching non-spherical granules, teach the idea of non-spherical granules and Cha exemplifies a method of forming "non-spherical granules."

Applicants respectfully traverse the assertions and conclusions of the Office Action in turn.

Teaching away and impermissible hindsight

Applicants respectfully traverse the conclusion that one of skill in the art would find it obvious to combine the acid of Francois with the granular formulation of Cha because (1) Francois teaches that acid should not be used in a granular formulation, and (2) impermissible hindsight is required to combine the acid of Francois with the granular formulation of Cha.

Francois teaches a liquid itraconazole preparation. Column 5, lines 24-25, 37-41. The itraconazole is fully dissolved in an acid-organic solvent. Column 3, lines 40-41. Francois teaches that acids in itraconazole preparations that are not fully dissolved are useless for oral administration. Column 1, lines 23-25. Francois further teaches that weaker acid preparations with co-solvents have problems with bioavailability and irreversible precipitation in the stomach. Column 1, lines 28-32. Francois also teaches that acidic formulations of itraconazole with cyclodextrin have unreliable absorption. Column 1, lines 32-38. Francois concludes the need for a formulation of itraconazole with good bioavailability and acceptable organoleptic properties has not been achieved with acid preparations. Column 1, lines 37-40.

Cha teaches a granular preparation of itraconazole. The granular preparation has improved solubility because of reduced particle size and amorphous crystallinity. Cha, column 1, lines 55-59. The granular formulation is dry and contains no organic solvent. *See* Cha, column 4, lines 7-8.

The Office Action concludes it would be obvious to combine the acid of Francois with the granules of Cha. Such a combination would require one of skill in the art to disregard Francois' direct teaching away from acids in granular preparations. Such a combination would also require employment of impermissible hindsight by gleaning knowledge only disclosed in the above-captioned application.

Francois teaches away from combining hydrochloric acid with granular preparations

"It is improper to combine references where the references teach away from their combination." *In re* Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983); MPEP § 2145(X)(D)(2). Francois teaches directly away from the use of an acid in the granular formulation of Cha for oral administration and concludes that good bioavailability and acceptable organoleptic properties has not been achieved with acid preparations:

> The development of efficacious pharmaceutical compositions of . . . itraconazole . . . is hampered considerably by the fact that said antifungals are only very sparingly soluble in water. The solubility and bioavailability of said compounds can be increased by complexation with cyclodextrins . . . . Alternatively, strongly acidic formulations . . . of itraconazole . . . can be formed in which the active ingredients are partially dissolved. Obviously such strongly acidic formulations are **useless** for **oral administration**. Aqueous formulations comprising a co-solvent such as PEG 400 completely dissolve itraconazole at pH 2.3-2.5. However, these acidic formulations **have problems** with regard to ease-of-preparation, acceptability, palatability and especially **bioavailability**: upon administration said formulations can **precipitate irreversibly**, e.g. in the stomach. Acidic formulations comprising cyclodextrin or a derivative thereof might appear an obvious alternative, but the mere combinations prove to **suffer from a number of similar problems**, in particular difficulty-of-preparation, lack of stability (shelf life) and palatability, and **unreliable absorption**. In short, there **still exists an important demand** for easily prepared formulations of

> antifungal agents with **good bioavailability** and **acceptable organoleptic properties** for oral administration.

Francois, column 1, lines, 14-40 *(emphasis added)*.

One of skill the art would conclude that Francois unambiguously rejects the use of acid to achieve solubility in any non-liquid formulation and would understand that the acid of Francois should not be combined with the granular formulation of Cha.

Impermissible hindsight required to combine acid and granular formulation

Hindsight using "knowledge gleaned from applicant's disclosure" is improper. *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971); MPEP § 2145(X)(A). Applicants respectfully submit it is impermissible hindsight to rely on Applicants' disclosure of a granular composition containing acid for improved bioavailability in support of combining Francois' liquid formulation dissolved in acid-organic solvent with Cha's dry, solid, granular formulation containing no acid and no organic solvent.

Cha teaches granules that expressly do not contain solvent and, as such, could not contain the acid solvent of Francois. *See* Cha, column 4, lines 7-8 and column 1, lines 55-59. Francois expressly teaches a liquid preparation, which is not granular and, as discussed above, teaches away from acid granular preparations. As a result, a combination of the teachings of Cha and Francois could in no way result in granules having acid content unless one improperly employed Applicants' express teaching that acid is an element of an itraconazole preparation with improved solubility.

Baert and Murai likewise do not provide a teaching or suggestion to use acid in a granular preparation

The other art cited in the Office Action, Baert and Murai, provide no additional teaching that an acid should be combined with a granular preparation to provide improved bioavailability. Baert teaches improved solubility with melt-extruded granular itraconazole in combination with croscarmelose, but provides no teaching or suggestion of the use of acid in a granular preparation. *See* Baert, column 3, lines 25-50. Murai teaches improved solubility using small granules and soluble additives in combination with

polyvinylpyrrolidone as an optional binder, but does not teach an acid or any method for adding acid to a granular preparation. *See* Murai at paragraph 32.

Since Cha and Francois together do not teach or suggest addition of the acid element to the granular element of the claims and Baert and Murai provide no additional teaching concerning these elements, Applicants respectfully submit the art cited in the Office Action does not render the claims obvious. Applicants, therefore, respectfully request the rejection be withdrawn.

The art does not teach non-spherical granules

The Office Action finally asserts that Cha exemplifies use of a fluid-bed granulator and, as such, must have inherently taught "non-spherical granules." None of the art cited in the Office Action expressly teaches "non-spherical granules" as a desired characteristic for improved solubility. Additionally, none of the art describes a granulation process that expressly results in "non-spherical granules."

Cha teaches the use of fluid-bed granulation; Cha does not provide a method of fluid granulation meant to achieve "non-spherical granules." There are a myriad of variables applicable to each phase of fluid-bed granulation and wide variability in size, shape and physicochemical formulation and structure can result from changes in these variables. *See* Rantanen J. *et al.*, Process Analysis of Fluidized Bed Granulation, AAPS PharmsciTech 2001: 2(4) article 21 (a copy is provided herewith). As such, simple exemplification of fluid-bed granulation by Cha—absent a teaching of how to achieve non-spherical granules or whether non-spherical granules were the result of the practiced method—should not be considered an exemplification of the use of "non-spherical granules."

Because none of the art teaches, suggests or inherently possesses "non-spherical granules," Applicants respectfully request this ground of rejection be withdrawn.

CONCLUSION

It is believed that the present claims are in conditions for allowance and Applicants earnestly request allowance. Extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit

Account No. 11-0600. The Examiner is invited to contact the undersigned attorney if necessary to expedite allowance.

Respectfully submitted,

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Dated: November 11, 2005 By: _____

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